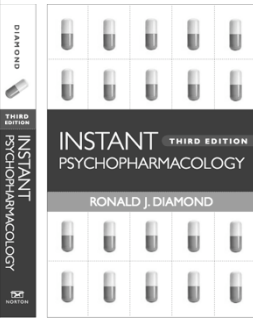


Antipsychotic Medications



INSTANT PSYCHOPHARMACOLOGY
 THIRD EDITION
 RONALD J. DIAMOND

Four out of five doctors recommend. . .

Think about side effects from the client's point of view

A common reason clients discontinue effective treatment is weight gain.

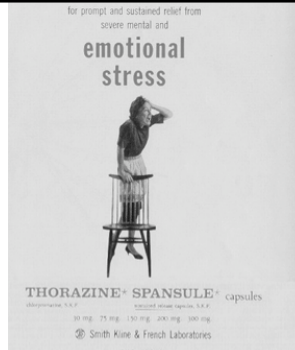
How much weight gain would you tolerate from a medication



Chlorpromazine [Thorazine]

“Major Tranquilizer”
 “Neuroleptic”
 “Antipsychotic”

Introduced 1953
 Ad from 1959



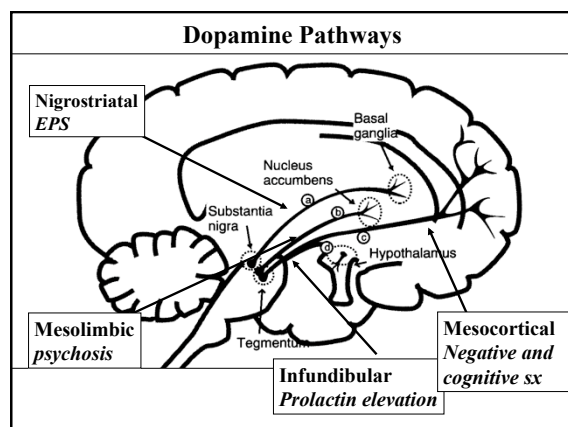
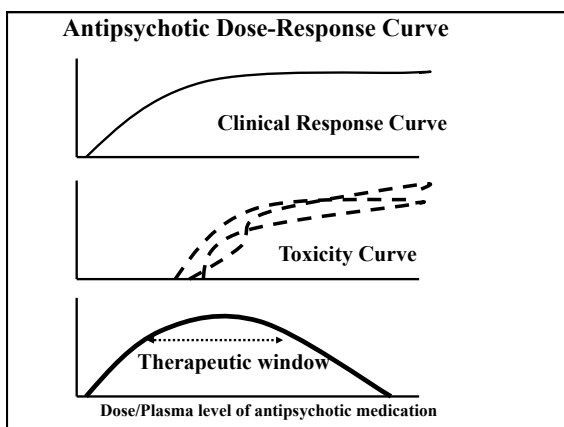
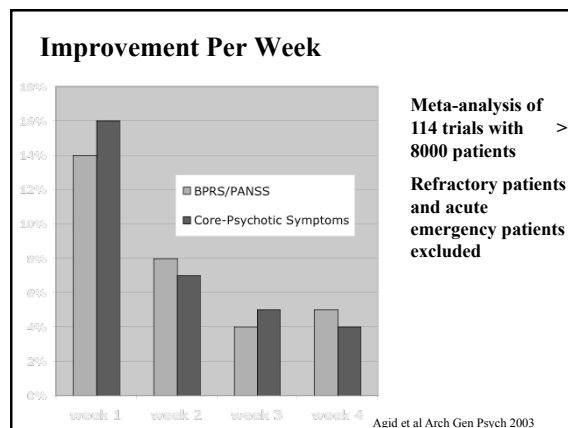
emotional stress

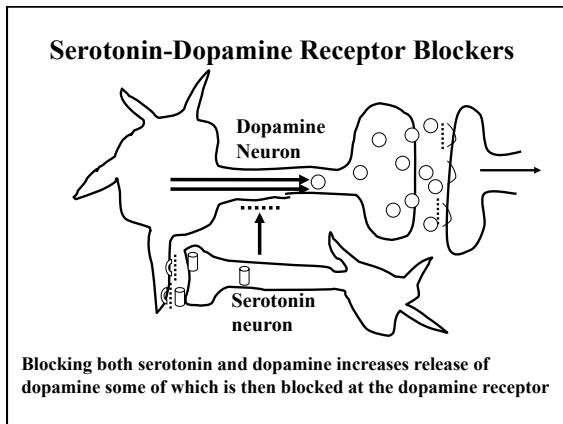
for prompt and sustained relief from severe mental and

THORAZINE® SPANSULE® capsules

20 mg 75 mg 100 mg 200 mg 300 mg

Smith Kline & French Laboratories



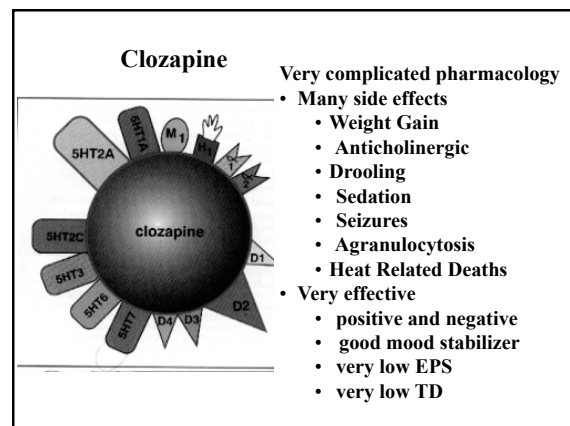
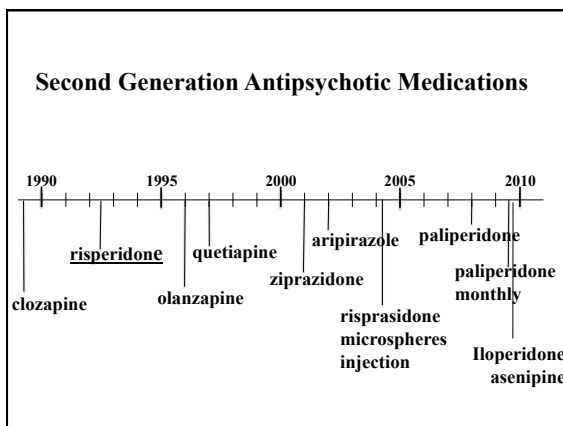


Receptor binding affinities of atypical antipsychotics

	K_i (nM)				
	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine
D_2	3.1	2.2	20	180	130
$5-HT_{2A}$	0.39	0.29	3.3	220	8.9
$5-HT_{2C}$	0.72	10	10	1400	17
$5-HT_{1A}$	2.5	210	2100	230	140
$5-HT_{1D}$	2.0	170	530	>5100	1700
α_1 -adrennergic	13	1.4	54	15	4.0
M_1 -muscarinic	5100	2800	4.7	100	1.8
H_1 -histaminergic	47	19	2.8	8.7	1.8

$K_i < 1$ nM — very high affinity; $K_i = 1-10$ nM — high; $K_i = 11-100$ nM — moderate; $K_i = 101-1000$ nM — low; $K_i > 1000$ nM — negligible.
 *Bovine binding affinity; †rat synaptosomes; all other affinities human.

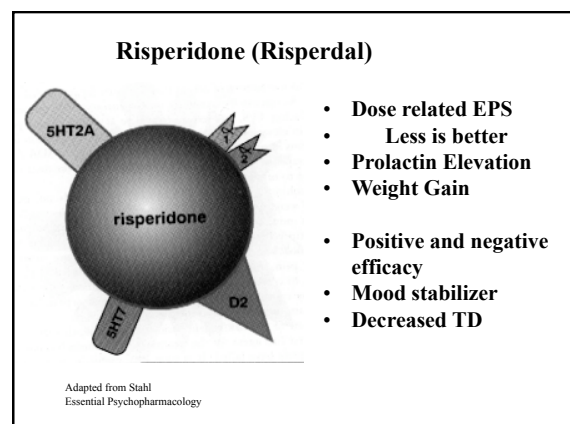
Zorn SH et al. *Interactive Monoaminergic Brain Disorders*. 1999;377-393.
 Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.



Clozapine Drug-Drug Interactions

Many important drug-drug interactions:

- Increase clozapine levels
 - Fluvoxamine (Luvox)
 - Fluoxetine (Prozac) or paroxetine (Paxil)
 - Risperidone
 - Grapefruit juice in large quantities
- Decrease clozapine levels
 - smoking



Risperidone drug-drug interactions

- Risperidone is metabolized by 2D6
- Drugs that inhibit 2D6, including fluoxetine (Prozac) and paroxetine (Paxil) can substantially increase risperidone levels

Paliperidone (Invega)

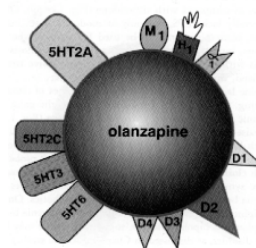
- Major metabolite of risperidone
- More gradual release than risperidone [but risperidone converted into paliperidone]
- Fewer drug-drug interactions (metabolized primarily in kidneys, little P450 interaction)
- More QTc prolongation [not significant]
- Similar prolactin elevation to risperidone
- ? Similar weight gain

Paliperidone Vs Risperidone

	Risperidone	Paliperidone
T _{max}	R: 1 hr 9-OH-R: 3 hrs	24 hrs
Peak to Trough Ratio (%)	38	125
T 1/2	3 hrs	23 hrs
Steady State	R: 1 day 9-OH-R: 5 days	4-5 days
CYP450 enzyme	2D6 - extensive	4 enzymes <10 % each

Docherty JP 2007 U.S. Psychiatric Congress

Olanzapine (Zyprexa)



Adapted from Stahl
 Essential Psychopharmacology

- Some dose related EPS
- Slight prolactin Elevation
- Big Weight Gain
- Diabetes (?)
- Somewhat sedating
- Positive and negative efficacy
- Mood stabilizer
- Decreased TD

Olanzapine drug-drug interactions

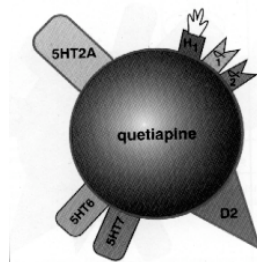
Decrease olanzapine levels

- Smoking
- Carbamazepine (Tegretol)

Increase olanzapine levels

- Fluvoxamine (Luvox), fluoxetine (Prozac)
- Erythromycin
- Grapefruit juice (in large quantity)

Quetiapine (Seroquel)



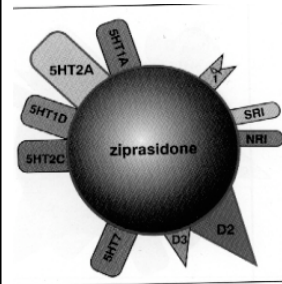
Adapted from Stahl
 Essential Psychopharmacology

- More is Better
- 400 mg up to 1200 mg
- Very low EPS
- Very low TD risk
- Some weight gain
- Sedating
- Needs dose titration to decrease dizziness
- Low dose may be useful in people with borderline disorder

Quetiapine and bipolar depression

- 2 trials support efficacy in bipolar depression [Boulder I and Boulder II]
- Norquetiapine (metabolite of quetiapine) potent inhibitor of norepinephrine transporter
- Blocks alpha-2 autoreceptors (as does mirtazapine)
- Stimulates 5-HT_{1A} receptors

Ziprasidone (Geodon)



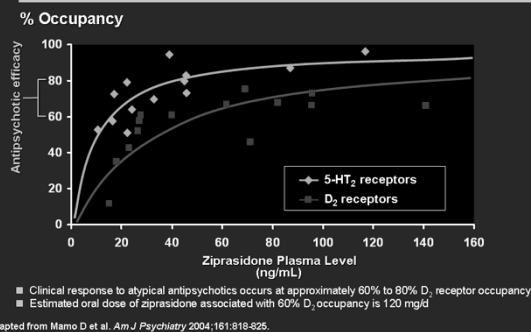
Newest antipsychotic
 NO WEIGHT GAIN
 Very low diabetes risk
 Higher dose often better than low

QTc prolongation
 Activating/agitating
 Antidepressant activity

Nausea, sleep disturbance
 EPS dose related

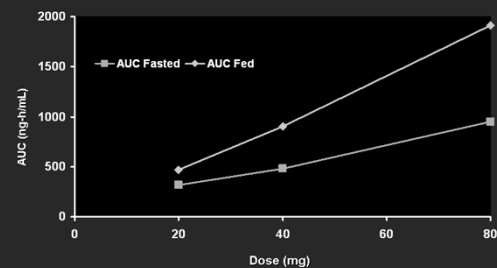
Adapted from Stahl
 Essential Psychopharmacology

Plasma Level vs % Receptor Occupancy at 12 Hours Postdose



Food Effect on Dose Dependence and Fasting PK: Study 006

Dose Ziprasidone With Food to Maximize Absorption

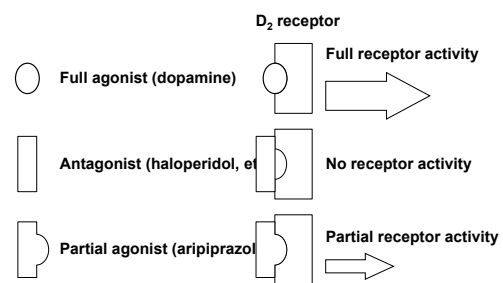


Data on file, Pfizer Inc.

Aripiprazole (Abilify)

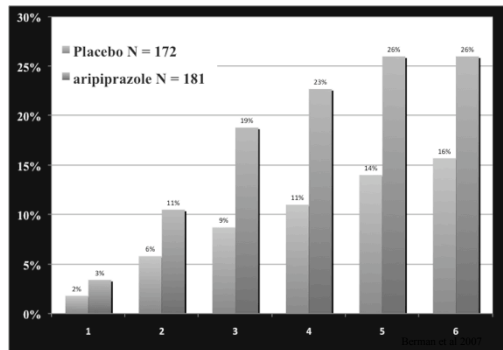
- Dopamine agonist/antagonist
- Appears to cause relatively little weight gain, little EPS, little sedation and little effect on heart function

Intrinsic Activity: Ability to Stimulate Receptors



Tamminga. *J Neural Transm*. 2002;109:411.

Remission rates of depression with aripiprazole augmentation



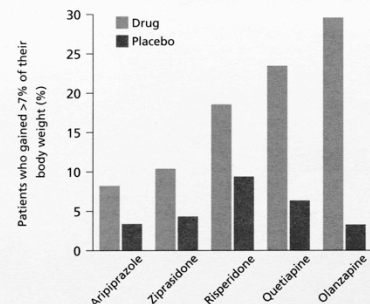
Iloperidone [Fanapt]

- Long complicated develop history
- Some weight gain, less EPS
- More similar to other second generation meds than different
- May have QTc prolongation
- Active comparator was ziprasidone

Asenapine

- Sublingual tablet
- 5HT 2D2 antagonist

Percentage of Patients With Clinically Significant Weight Gain in Short-Term Placebo-Controlled Trials



Source: Haddad PM. Weight change with atypical antipsychotics in the treatment of schizophrenia. J Psychopharmacol. 2005;19(suppl 6):16-27. Reprinted with permission.

1st Generation Antipsychotic Medications

Examples

- fluphenazine (Prolixin)
- haloperidol (Haldol)
- Both available as long acting injection
- Traditional D₂ blocker may (??) work better in rare patients
- Much less expensive
- “Semi-traditional medications”
- Loxapine (Loxitane)

Antipsychotic Medications

Traditional Indications

- Schizophrenia
- Mania/ mood stabilization
- Agitated or psychotic depression
- Psychosis associated with dementia [black box warning]
- Drug induced psychosis

Other possible indications

- Agitation
- Severe OCD
- Anxiety with cognitive disorganization

Antipsychotic Side Effects
 EPS (Extrapyramidal [muscle] side effects)

- Dytonias (muscle cramps)
- Tremor--coarse Parkinsonian type tremor
- Akinesia--decreased movement/spontaneity
- Akathisia--motor restlessness
- Tardive Dyskinesia: MAY BE PERMANENT

Antipsychotic Side Effects
 common--not life threatening

- Psychotoxic side effects
 - Depression, sedation, confusion, dysphoria
- Anticholinergic
 - Dry mouth, constipation, blurred vision, memory impairment, confusion
- Alpha-adrenergic
 - dizziness
- Increase Prolactin
 - Breast engorgement, sexual side effects

Antipsychotic Side Effects
 Rare but dangerous

- Blood dyscrasias: agranulocytosis
- NMS: neuroleptic malignant syndrome
- Temperature regulation: fatal heat stroke
- Cardiovascular effects: sudden death
- Seizures

NMS: Neuroleptic Malignant Syndrome

Usually within 30 days of new medication or ↑ dose

- Hyperthermia (fever)
- Muscle rigidity
- Tremor, myoclonus (muscle jerks)
- Confusion, stupor
- Increased heart rate, labile blood pressure
- Rapid breathing, shortness of breath
- Sweating, sialorrhea, incontinence
- Elevated CPK, leukocytosis, metabolic acidosis

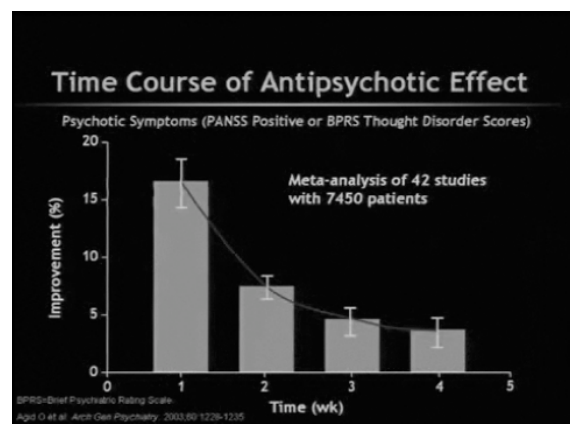
Long-acting injectable antipsychotics

1st Generation

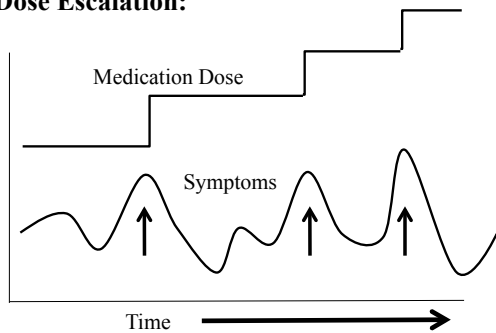
- Fluphenazine deconate [Prolixin Deconate]
- Haloperidol deconate [Haldol Deconate]

2nd generation

- Risperidone [Risperdal Consta]
- Paliperidone palmitate [monthly]
- Olanzapine pamoate [monthly]



Dose Escalation:



Second Generation Antipsychotics: are they worth the cost?

- CATIE
- CUTLESS
- Long-term VA study